

Clinical Topics

First clinical use of penicillin

CHARLES FLETCHER

In January 1941, when Hitler's bombs were raining down every night on London, Oxford was a peaceful city, especially when a full moon gleamed down on the otherwise unlit streets. I had just completed six months as house physician to Professor Witts, and had been appointed a Nuffield research fellow—the equivalent of what would now be called a lecturer in an academic medical unit. I had not yet decided on any research project, and I knocked on the professor's door to discuss this with him. There was a bespectacled man in his room whom he introduced as Professor Howard Florey, who had come to ask for help with the first clinical trials of penicillin. I had, of course, read about its potent antibacterial power in mice in a recent article in the *Lancet*.¹ To my delight he asked if I would like to take this on and, of course, I readily agreed.

It was characteristic of Florey that the first thing that he did was to ask me to go over to the Dunn Laboratory, where all the penicillin work had been carried out, to meet the rest of his team. Ernst Chain—small, dark, excitable, bubbling with enthusiasm—showed me his apparatus for freeze drying the extracts of penicillin to produce a yellow powder. Norman Heatley quietly showed me the stacks of bed pans in which he had succeeded in producing just enough penicillin to make it possible to consider starting clinical trials and his ingenious extraction columns for getting the penicillin out of the culture medium into aqueous solution. Professor A D Gardner, the oldest member of the team, was in charge of bacteriology with E D Abraham also working on the chemistry. During the rest of year I was always welcomed over there to see all that was going on.

Florey explained that although penicillin had been found to be entirely harmless to leucocytes, tissue cultures, and a wide variety of laboratory animals, he did not want to risk giving the first injection to a healthy volunteer in case of some unique adverse reaction in man. So he asked me to find a patient with some inevitably fatal disorder who might be willing to help. There were no ethical committees in those days that had to be consulted, so I looked around the wards and found a pleasant 50 year old woman with disseminated breast cancer who had not long to live. I explained to her that I wanted to try a new medicine that could be of value to many people, and asked if she would agree to a test injection of it. This she readily did.

First injection

Florey and Witts came with me on 17 January to witness the first injection of 100 mg (about 5000 units) of penicillin, which was expected to produce a bactericidal concentration in the blood. I

gave it slowly into an antecubital vein, and the patient at once said that she had a curious musty taste in her mouth but suffered no other immediate harm. A blood sample taken shortly afterwards was bactericidal. A few hours later, however, she developed a rigor and her temperature rose for a few hours, but there were no other ill effects. Before clinical trials could be carried out the pyrogen was removed by further purification and rabbits were used to ensure that no pyrogen remained.

My first job was to try out various routes of administration on several volunteer patients. These just confirmed what had already been shown by animal studies, that penicillin was destroyed in the stomach, and oral administration in man also failed. Penicillin was present in blood and urine after administration with a duodenal tube but rectal administration was useless. Detectable blood concentrations were only transient after a single intravenous injection. We decided that the best route of administration would be by hourly injection into a continuous, slow running, citrate saline intravenous drip, for the high peak blood concentrations should encourage diffusion into the tissues and into collections of pus. The standard technique for such infusions then was to dissect out a superficial vein and tie in a small swan necked cannula. Simple screw caps were the only mechanism available to control the rate of flow, and they were pretty erratic. Fortunately, Marriott and Kekwick had just described a reliable flow control device using loops of capillary tubing about five inches (13 cm) long connected together by T pieces having rubber tubes with screw clips between each loop.² I quickly made up two or three of these gadgets and they functioned admirably. Each penicillin injection could be flushed in by brief release of all the clips to short circuit the capillary tubes. By this means the intravenous infusions were kept to a rate of roughly 10 ml an hour.

The time had now come to find a suitable patient for the first test of the therapeutic power of penicillin in man. Every hospital then had a "septic" ward, filled with patients with chronic discharging abscesses, sinuses, septic joints, and sometimes meningitis. Patients with staphylococcal infections would be ideal because sulphonamides had no effect on them and were inactivated by pus. In the septic ward at the Radcliffe Infirmary there was then an unfortunate policeman aged 43 who had had a sore on his lips four months previously from which he had developed a combined staphylococcal and streptococcal septicaemia. He had multiple abscesses on his face and his orbits (for which one eye had been removed): he also had osteomyelitis of his right humerus with discharging sinuses, and abscesses in his lungs. He was in great pain and was desperately and pathetically ill. There was all to gain for him in a trial of penicillin and nothing to lose.

Penicillin treatment was started on 12 February 1941, with 200 mg (10 000 units) intravenously initially and then 300 mg every three hours. All the patient's urine was collected, and each morning I took it over to the Dunn Laboratory on my bicycle so that the excreted penicillin could be extracted to be used again. There I was always eagerly met by Florey and Chain and other members of the team. On the first day I was able to report that for the first time throughout his illness the patient was beginning to feel a little better. Four days later there was a striking improve-

London SE11 4SN

CHARLES FLETCHER, MD, FRCP, emeritus professor of clinical epidemiology, University of London

Correspondence to: 14 West Square, London SE11 4SN.

ment, and after five days the patient was vastly better, afebrile, and eating well, and there was obvious resolution of the abscesses on his face and scalp and in his right orbit. But, alas, the supply of penicillin was exhausted: the poor man gradually deteriorated and died a month later. The total dose given over five days had been only 220 000 units, much too small a dose, as we now know, to have been able to overcome such extensive infection; but there was no doubt about the temporary clinical improvement, and, most importantly, there had been no sort of toxic effect during the five days of continuous administration of penicillin. This remarkable freedom from side effects, apart from allergy, has remained one of penicillin's most fortunate features.

Concentrating on children and localised infections

We then decided to avoid using large amounts of the precious penicillin by concentrating on children and localised infections. The results in the next patient were rather equivocal. He was an ill looking febrile boy aged 15 who had had an operation for a slipped femoral epiphysis and whose wound had become infected with a streptococcus resistant to sulphonamides. Treatment with penicillin was started on 22 February. His fever responded and he felt and looked much better, but the local infection was not altered and for some obscure reason his blood never showed more than slight antibacterial activity.

The third patient I chose for treatment was a man of 48 in the septic ward who had developed a carbuncle about four inches (10 cm) in diameter on his back over five days. Few doctors nowadays can have seen a carbuncle like this. It consisted of an indurated, red area over one scapula, and there were five sinuses in it all discharging staphylococcal pus. He had been given the only treatment that was then available—kaolin and magnesium sulphate poultices—and the natural course would be slow, painful resolution over several weeks. The effect of penicillin was dramatic. After five days, during which 6 g of penicillin (about 0.3 million units) had been given, the carbuncle had just melted away and there had not been the slightest toxic effect. The penicillin had achieved what had never been seen before—rapid resolution of extensive purulent induration due to a staphylococcus.

The patient who remains most clearly in my memory was the next one to be treated, a boy aged 4½ years. He had had a septic spot on his left eyelid five weeks previously, which had led to cavernous sinus thrombosis. This was a condition that, as a student, I had feared more than anything else with its 100% fatality and painful course. The boy had bilateral proptosis and oedema of both his eyes, which he could not open. He had a high fever was semicomatose and incontinent, and there had been no response to sulphapyridine. He had only a few hours to live. His father had cherished the hope that this little boy would grow into a man to help him on his farm and was desolate. After two days of penicillin there were already signs of improvement, and after a week's treatment with a total of 7.2 g (about 0.36 million units) the boy was sitting up fully conscious, even playing with his toys. Three days later he had no fever and his eye movements were becoming normal. But then there was sudden tragedy: he developed convulsions; a lumbar puncture showed heavily blood stained fluid, and he died. This was a tragic outcome, but the necropsy showed that the infection in the cavernous sinus had been cured and that the abscesses in the lungs were resolving and free from pus. Death had been due to rupture of a mycotic aneurysm of the carotid artery. So, although the boy died because treatment had been started too late, penicillin had cured the infection for which it had been given.

The final patient whom I treated with intravenous penicillin was another boy, aged 14, with staphylococcal osteomyelitis of the femur with a positive blood culture: a condition that then had a fatal prognosis. This boy was given 17.2 g intravenously over two weeks (about 0.86 million units daily) and was completely cured. In those days this could well be described as a clinical miracle.

The final patient to have systemic treatment was quite different from the others. He was a baby boy, 6 months old, who was

seriously ill with a staphylococcal urinary infection for which sulphapyridine had been tried but had led to severe neutropenia, and on which ammonium mandelate had also had no effect. I tried but failed to get a tube into his duodenum, so oral treatment was given for one week, together with sodium bicarbonate to inhibit gastric digestion. During this time all urine specimens contained effective concentrations of penicillin: the infection was abolished and the baby recovered.

This small series of clinical cases gave, of course, no proof of the astonishing power of penicillin that we now recognise, but they did establish that it could cure fatal staphylococcal septicaemia and could act, unlike the sulphonamides, in the presence of pus. It seemed almost certain that it would be equally effective against all the Gram positive bacteria that it inhibited in the laboratory. The evidence was in any case sufficient for Florey and Heatley to be flown over to the United States of America to initiate the commercial production of penicillin that provided enough to save the allied forces from sepsis and gas gangrene in the last two years of the second world war.

Member of Florey's team

It is difficult to convey the excitement of actually witnessing the amazing power of penicillin over infections for which there had previously been no effective treatment. I could not then imagine the transformation of medicine and surgery that penicillin would produce. But I did glimpse the disappearance of the chambers of horrors, which seems the best way to describe those old septic wards, and could see that we should never again have to fear the streptococcus, whose eclipse Garrod described so vividly, or the more deadly staphylococcus.³ There was also the excitement of being counted for a short while as a member of Florey's team, for that was how he treated me, a mere clinical technician. My name was to appear in its appropriate alphabetic position in the list of authors of the first published account of these early clinical trials.⁴ Later he invited me to a celebration dinner, which he arranged at Magdalen College, and my name appears on the tablet in the penicillin memorial rose garden outside the Oxford botanical gardens.

Florey was most friendly to me despite his laconic reserve, which contrasted greatly with Chain's effusiveness. He had a quiet, impish sense of humour, which often flashed out with a sort of short grunt. When the merits of penicillin had become quite clear I said to him one day rather plitudinously, "It must be wonderful to have made a discovery like this." He paused for a moment and then said, "Yes, one can't expect this sort of thing to happen to one more than once in a lifetime." I felt that once would be more than enough for me. Macfarlane has recounted how Fleming came to get all the credit for the triumph of penicillin while Florey and his team remained almost unknown except among their scientific peers.⁵ While I was still at Oxford—I left for another appointment in November 1941—Florey showed me a letter that he had just received from the appeals secretary at St Mary's Hospital, London. It started, "You may have heard of the discovery of penicillin by Professor Fleming at St Mary's Hospital," and it went on to invite him to buy tickets at two guineas each for a charitable show in London. "I'm going to have this framed," he said, with a chortle. He did, and he hung it for all to see in the entrance to the Dunn Laboratories.

I met Fleming only once, in 1954, when BBC *Panorama* decided to include an item on the discovery of penicillin in what was then a magazine programme. They asked me to interview Fleming without knowing that I had had any connection with penicillin's earliest clinical use. Any resentment that I had hitherto felt about Fleming's unmerited fame was melted by his simple humble attitude to the part that he had played in the story, and in the programme he gave full credit to the Oxford team. This programme was broadcast just a fortnight before he died and showed him in characteristic mood. It is now part of the BBC's archives.

I still occasionally shine in the reflected fame of Florey and his

team at Oxford when I am introduced before a lecture as "the man who gave the first injection of penicillin." When this happens I think with gratitude of that quiet moment in the ward at the Radcliffe Infirmary with Florey and Witts, to both of whom I owe so much, standing by and I think of Mrs Elva Akers offering me her vein for the injection.

References

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Penicillin: early trials in war casualties

SIR IAN FRASER

About 40 years ago the trials of penicillin on war casualties in the forward area began. The original team consisted of a surgeon and a bacteriologist. The surgeon (IF) had to be old enough to have had some experience of the failure of the sulphonamides and other antiseptic drugs, but young enough to be able to wade ashore if necessary during the various invasions. Probably more important was the choice of an expert bacteriologist, Major Scott-Thompson, later professor of bacteriology in Cardiff. The team was under the overall control of the Medical Research Council and the Royal Army Medical Corps.

The trials could not have been sooner, because in Britain penicillin was in such short supply, so when the time came all the penicillin in Oxford was needed. What there was was mostly in the form of calcium salt suitable only as a surface dressing and perhaps enough for 100 patients, while of the sodium salt suitable for injection there was enough for only two or three dozen patients.

Serendipity seems to have accompanied penicillin in all its stages right from the accidental discovery by Alexander Fleming in 1928 of a fungus of incredible rarity. Ten years later at Oxford Florey decided to try to extract pure penicillin from "the broth" and produce something that could be of real clinical value. A Jewish evacuee, Ernst Chain, had been working with him for some time; he was a man with an international reputation in the study of enzymes. Together they formed a useful partnership. A further piece of luck was the choice of the mouse as the laboratory research animal: had they chosen the guinea pig it might have been quite a different story. Another piece of good fortune was that Florey had as his partner in the clinical trials Hugh Cairns, a neurosurgeon. Neurosurgery was ideal for the experiment, for in abdominal surgery there were many highly resistant organisms, which might have delayed the progress in this research. Fleming had put penicillin on the map, but Florey really put it on the market. Those of us involved in the early stages of this work could sense the tension at times in the relationship between these two great men.

The timing of the experiment was, as far as the war was concerned, also important. Penicillin became available just at the end of the eighth army desert campaign (February 1943) and was therefore in full swing and ready for use by the first army for the invasion of Sicily and Italy when the attack took place through the "soft underbelly of the Axis."

Our team was given a two week crash course in Oxford, when we saw the drug being produced and were taught the methods of using it as well as how to organise a mobile laboratory in the forward area. We worked with Florey at close quarters. He had turned his university department almost into a factory. Mrs Ethel Florey was busy on her bicycle each day, collecting the overnight urine from the various hospitals from patients taking parenteral



penicillin. The more sophisticated among us called this "the morning milk round," the less so called it "the P patrol." This urine contained two thirds of what had been given to the patient, and of this one half could be retrieved—recycling, so to speak. One great advantage was that this penicillin retrieved from the urine had been freed from the "gubbins" of the culture medium, which was some 90% of the total that the patient had received at the time of the original injection. This purified penicillin was very popular as its injection was virtually painless and free from the short but awful reaction that the impure penicillin produced. At that time penicillin was a brown powder and in solution it looked rather like dilute mustard, and when injected it felt like it too.

The penicillin research team were given instructions not to try the drug out on diseases that had already been fully researched—for instance, osteomyelitis, malignant endocarditis, venereal disease—or indeed on enemy casualties. The embargo on venereal disease I readily agreed to as it is not a disease one acquires normally when wading ashore on foreign soil. I did, however,